In This Issue . . .

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Gamma-Interferon Induces Adhesion Molecule Expression in Skin

The lymphokines are the two-edged swords of the immune system. They are needed for the initiation and maintenance of normal immune responses, but they can also contribute to the development of inflammatory diseases. In this issue, Jonathan Barker, Michael Allen, and Donald MacDonald of Guy's Hospital in London, England, describe one way in which the lymphokine gamma-interferon may contribute to inflammatory skin conditions. The researchers have found that it induces the expression of the adhesion molecules that mediate many responses of the lymphocytes of the immune system.

The current study differs from past work in that the London workers examined gamma-interferon's effects in the skin of living human beings. "A lot of studies have been done over the last 4 years looking at the effects of gamma-interferon in vitro, and the results extrapolated to what was going on in vivo in inflammatory diseases" Barker says, "We looked at the in vivo effects."

To do this, Barker and his colleagues injected gamma-interferon daily for 3 days into the skin of 14 volunteers. On the sixth day, they took skin biopsies and stained them with monoclonal antibodies for LFA-1 (lymphocyte function associated antigen 1) and ICAM-1 (intercellular adhesion molecule 1). The interaction between LFA-1 on lymphocytes and ICAM-1 on other cells helps to trigger lymphocyte activation.

The researchers found that gamma-interferon is a potent inducer of ICAM-1 expression on both keratinocytes and endothelial cells in the skin. "In normal skin you don't see ICAM-1 on keratinocytes," Barker points out. In addition, the lymphokine induced LFA-1 expression by lymphocytes. Comparable changes in adhesion molecule expression had been found in the in vitro studies, but the in vivo work also showed that the changes had physiologic consequences, may acting to draw lymphocytes into the skin. "There was a lymphocyte-rich infiltrate predominantly in two places — around the endothelial cells and basal keratinocytes expressing the ICAM-1," Barker says.

The gamma-interferon also stimulated the expression of LFA-1 on epidermal Langerhans cells, the antigen-presenting cells of the skin, which also participate in lymphocyte activation. "Gamma-interferon, when injected into the skin, can produce many of the changes you see in inflammatory skin disease, suggesting that it is an important cytokine in these diseases," Barker explains.

The findings may have clinical implications. It may be possible to design drugs that inhibit gamma-interferon's stimulation of the adhesion molecule expression or prevent the molecules from interacting with one another, thereby interfering with the inflammatory changes induced by the lymphokine.

Evidence Found for New Antigen-Presenting Cells in the Dermis

A great deal of evidence points to the epidermal Langerhans cells as the primary antigen-presenting cells of the skin. As such they play a critical role in the triggering of contact hypersensitivity reactions. But new evidence, described in this issue by J. Wayne Streilein of the University of Miami School of Medicine, indicates that the Langerhans cell is not the only skin cell that can present antigens and elicit contact hypersensitivity reactions. Some other, as yet unidentified, cell located in the dermis also has this ability. "The experiment reveals that in certain circumstances you can bypass the Langerhans cells," Streilein says.

The finding came as a big surprise. Streilein was following up on earlier experiments showing that contact hypersensitivity is suppressed in some strains of mice that have been treated with low-dose UVB, but not in others. This difference could not be explained by a differential effect of the radiation on the skin's Langerhans cells. They were severely depleted in all the irradiated animals. Streilein hypothesized that the resistant strains might have a second, UVB-insensitive pathway of antigen presentation that is lacking in the susceptible animals.

The current experiments attempted to see if that was the case. Streilein used cellophane tape to strip the epidermis and upper dermis from the skin of both susceptible and resistant animals, thereby removing the animals' Langerhans cells. If his hypothesis was correct, then the skin-stripping should have had the same effect as UVB irradiation on the susceptible animals. They should not have been able to develop a contact hypersensitivity reaction.

Unexpectedly, however, all the animals developed contact hypersensitivity responses. "There must be more than one way to induce contact hypersensitivity," Streilein says. "In the absolute absence of Langerhans cells, there must be another cell in the dermis — not the epidermis — that can present antigen." The dermal antigen-presenting cell has not yet been identified, however.

The new findings necessitate a re-evaluatin of the hypothesis that the ability of UVB radiation to suppress contact hypersensitivity in some mouse strains is mediated by its effects on epidermal Langerhans cells in those animals. As mentioned previously, the radiation affects the cells just as severely in the resistant animals as in the susceptible ones, and both groups of animals have the new Langerhans cell-independent pathway for triggering contact hypersensitivity. It may therefore be necessary to look elsewhere for an explanation of the effects of UVB on contact hypersensitivity, Streilein says. Although his experiments failed to answer his original question, they have opened an unexpected new line of inquiry to pursue.

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New Light Shed on the Therapeutic Effects of the Retinoids

Two papers in this issue explore the therapeutic actions of the retinoids. One, from researchers at the University of Michigan School of Medicine in Ann Arbor, may help to explain the apparently paradoxical actions of the agents on skin cell proliferation — they may inhibit keratinocyte growth in some circumstance, but stimulate it in others. The second paper, from a group at the Hopital Henri-Mondor in Creteil, France, looks at another aspect of retinoid action, namely, the drugs' immune effects, which may contribute to their efficacy in treating inflammatory skin conditions, including psoriasis.

Most researchers have found that all-trans retinoid inhibits the growth of cultured keratinocytes, says James Varani of the Michigan group. This result is consistent with the therapeutic efficacy of the retinoids in psoriasis, which is characterized by higher than normal keratinocyte growth. But it is hard to reconcile with the retinoids' effects on photoaged skin where the retinoids reduce fine wrinkles, apparently by stimulating the growth of the skin cells.

Varani and his Michigan colleagues, Brian Nickoloff, Vishva Dixit, Raj Mitra, and John Voorhees, have now found that the growth effects of all-trans retinoic acid on cultured keratinocytes vary, depending on the initial proliferative state of the cells. "We looked at all-trans retinoic acid under the conditions other people have used, when the cells are rapidly proliferating," Varani says. "Under these conditions, it indeed inhibits proliferation."

However, when the Michigan workers removed the growth factors from the medium used for culturing the keratinocytes, they obtained a different result. "The cells cease proliferating and go into a quasi-differentiated state. These cells are stimulated by the retinoic acid," Varani explains.

The findings may explain the retinoids' discordant effects in vivo, the Michigan workers suggest. The proliferative action of the drugs in photoaged skin occurs, Varani notes, not in the basal cell layer where the cells are normally dividing, but in the layer above where growth has ceased. These cells might therefore proliferate in response to retinoid treatment. In contrast, the dividing keratinocytes of psoriatic skin might respond with slowed cell division, as the cultured cells do.

Varani and his colleagues also found that the all-trans retinoid decreases the production by keratinocytes of thrombospondin and fibronectin, adhesion proteins that help to hold skin and other cells together. Reduced production of these proteins may contribute to the increased fragility seen in the skin of psoriasis patients undergoing treatment with the retinoids.

Not only do the retinoids alter keratinocyte growth, but they also have a number of effects on immune responses. Some of these may contribute to the usefulness of the drugs in treating psoriasis, which is characterized by an inflammatory infiltrate as well as by enhanced keratinocyte growth, and other inflammatory conditions such as lichen planus. But just as with the keratinocyte growth situation, the retinoids have both stimulatory and inhibitory immune effects, a situation that complicates efforts to understand how they improve inflammatory skin diseases.

The group from the Hopital Henri-Mondor, which includes Patrick Dupuy, Martine Bagot, Michele Heslan, and Louis Dubertret, now reports, however, that several synthetic retinoids inhibit the ability of epidermal cells to stimulate the growth of lymphocytes when the two cell-types are grown together in culture. The retinoids also decreased the cell-killing abilities of the lymphocytes. Since lymphocyte activity contributes to inflammatory responses, these inhibitory effects of the retinoids may help to explain the drugs' beneficial action in inflammatory skin disease, the researchers suggest.

The retinoids may decrease lymphocyte proliferation by suppressing antigen presentation by the epidermal cells, an essential step in lymphocyte activation. The French workers see the inhibitory effects of the retinoids only when they expose the epidermal cells to the drugs before the cells are mixed with the target lymphocytes. This suggests that the retinoids act through the epidermal cells, although Dupuy and his colleagues have not yet identified the specific way in which the drugs affect epidermal cell function.